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SJÖGREN'S SYNDROME[1]

ANGUS L. MacLEAN

In 1924 Stock (1) recognized dryness of the eyes as a cause of certain cases of filamentary keratitis. In 1930 Duke Elder (2) coined the new term "keratoconjunctivitis sicca" for this condition. About the same time it was suspected by Schoninger (3), Scheerer (4), Betsch (5) and Isakowitz (6) that the decreased function of the lacrimal gland in these patients might be a manifestation of systemic disturbance. In 1933 Sjögren's classic monograph (7a) on this subject appeared and his name is given to the syndrome of keratoconjunctivitis sicca, laryngopharyngitis sicca, and enlargement of the parotid glands.

ETIOLOGY

As was pointed out by Albrich (8), there is no satisfactory explanation of this condition. It seems to be part of a general systemic disturbance involving the lacrimal and salivary glands, and is frequently associated with other evidences of chronic systemic infection, such as arthritis, anemia, lymphocytosis, and increased sedimentation rate. The accompanying diminished nasoocular reflex, catarrh of the upper respiratory tract, achylia, suppression of sweat excretion, and bilaterality of the symptoms led the Dalsgaard-Nielsens (9) and Bruce (11) to ascribe the condition to a disturbance of the sympathetic nervous system. Because of the similarity of the ocular lesions to those of xerophthalmia, it has been thought by some to be due to avitaminosis. In one of the cases in our series (Case II) an earlier medical diagnosis of avitaminosis had been made, but liberal amounts of vitamins failed to prevent development of the classical clinical picture of Sjögren's syndrome. That the endocrine system may play a part in the production of the symptoms has long been suspected. As most cases occur in women usually at or near the menopause, the endocrines have been considered by many authors to be responsible. The condition does occur, however, before the climacteric. In Case III in our series the symptoms developed long before this period and the menstrual flow

[1] From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University.

was normal. In Case I, however, the symptoms commenced at the age of twenty-five, five years after panhysterectomy with artificial menopause. Hossos (quoted by VonGrosz (10), and Bruce (11)) removed the lacrimal glands from a rabbit, but no keratitis appeared until the ovaries also were removed. Krasso (12) reported the onset of keratoconjunctivitis sicca following oophorectomy. Lisch (13), on the other hand, pointed out that the signs of glandular involvement sometimes antedate the appearance of the ocular symptoms by several years, and that the association of the menopause with the appearance of the symptoms in the eyes may be entirely coincidental. Sjögren (7b) stated that there is no evidence to support the theory of allergic-anaphylactic disturbance and believed that the condition is due to an infection carried by the blood stream. In Case I the skin tests showed only a hypersensitivity to tuberculin, and desensitization failed to cause any improvement in the symptoms. P. Knapp (14) believed the condition to be a result of acute rheumatic fever. All three of the patients in our series had chronic rheumatoid arthritis. Bassalino (15) thought that the syndrome is due to suprarenal insufficiency. Syphilis and gonorrhea have been reported only once, and then in the same patient.

SYMPTOMS AND PHYSICAL FINDINGS

The patients complain of burning, pricking, and smarting of the eyes, and sometimes of diminished visual acuity. Frequently, but by no means invariably, this condition is accompanied by dryness of the eyes. Photophobia is often present. The patients sometimes complain of the characteristic stringy mucoid discharge and have difficulty in irrigating it away. Where the mucus is adherent to the bulbar conjunctiva it stains with argyrol or rose bengal, and can readily be seen.

The parotid glands, first one and then the other, swell gradually. The swelling is usually firm, but only occasionally tender. Regression generally occurs in periods varying from a week to several months, but occasionally the swelling is permanent. The mouth is dry and in some cases fissures develop on the tongue and lips. The dryness extends to the nose, pharynx, larynx and nasal sinuses.

The classical picture of dry eyes, dry mouth, and swollen parotid glands is not always complete. The ocular condition sometimes does

not appear for several years after onset of the other symptoms or it may be the only sign of the disease; when present, however, it seems to cause the most distress. Dry, ropy secretion, with shreds adhering

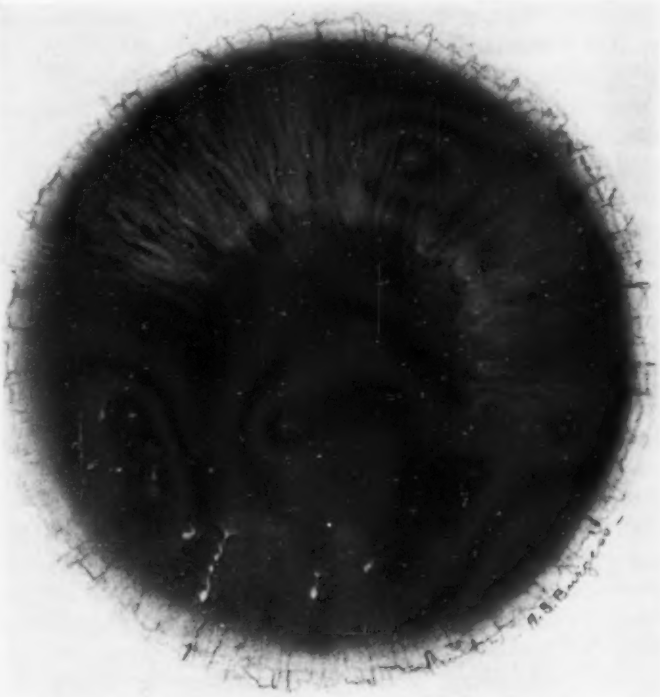

FIG. 1. PHOTOGRAPH OF A DRAWING OF THE CORNEA IN CASE 2

Note (1) the superficial haziness of the lower half of the cornea, (2) epithelial filaments, attached at one end, free and knob like at the other, (3) defects (staining areas) in the epithelium.

to the corneal epithelium, is a constant observation and is seen in practically no other condition. Fine epithelial filaments may be present (Fig. 1). In most cases there is diffuse, irregular, superficial staining of the cornea when fluorescein or other stains are used. Often clear regions are seen between deeply stained areas. Sensitivity is

usually diminished. The conjunctiva may appear almost normal but is usually congested, and a foamy secretion is often found at the canthi. The eyes sometimes look dry and may be flecked with meibomian secretion, but more often, absence of moisture is not apparent on inspection. This can be determined by means of a special filter paper test which will be described later. Seldom is the bacterial flora found to be anything but normal.

Complications are rare. Sjögren (7a) noted an instance of pannus formation, and another of perforating ulcer. In one of Bruce's patients a dense corneal opacity developed.

Associated Conditions.—Arthritis, usually of the extremities, is frequently present. Dental caries is often seen. Anaemia, achylia, and achlorhydria have been found and cyanosis of the hands and feet is a common complaint. Dryness of the skin, from involvement of the sweat glands is frequently observed.

PATHOLOGY

The microscopic pathology has been carefully studied by Sjögren. There are no other pathological reports on this condition in the literature.

According to Sjögren, the lacrimal and salivary (parotid, submaxillary and sublingual) glands, in all cases examined at autopsy or by biopsy, showed striking atrophy and some chronic inflammation with eosinophiles and scarring. In some cases there was cystic dilatation of the ducts. No giant cells were found.

Cornea.—The epithelium was normal in some areas, thinned or absent in others. Where filaments occurred, they were formed of the external portions of the epithelial layer or of whole desquamated epithelium. Connective tissue ingrowths beneath the epithelium and degenerated foci in the parenchyma were occasionally found.

Conjunctiva.—There was early destruction of elastic tissue and edema of the epithelium. All the cases showed infiltration with round cells and eosinophiles, and scarring. The mucous glands (goblet cells) were lacking generally but were present in large numbers in the lower fornix.

DIFFERENTIAL DIAGNOSIS

1. *Xerophthalmia due to A-Avitaminosis.*—In most of the reported cases of keratoconjunctivitis sicca there was no obvious dietary insuffi-

ciency (11). One of our patients was suspected of having avitaminosis. In another typical case, biophotometry and other tests failed to reveal any lack of Vitamin A. None of our patients had night blindness and none was benefited by the administration of Vitamin A. Furthermore, the ocular lesions are different in the two conditions, and deficient lacrimal secretion is not usually found in xerophthalmia.

2. *Chronic Conjunctivitis.*—From the symptoms and gross examination alone, many cases of keratoconjunctivitis sicca may easily be, and undoubtedly often are, diagnosed as chronic conjunctivitis. Slit-lamp examination after instillation of fluorescein and the Schirmer test will establish the diagnosis. Furthermore, in most cases of chronic conjunctivitis, pathologic bacteria are usually found.

3. *Trachoma.*—In extreme cases of keratoconjunctivitis sicca the conjunctiva may be so thick and velvety as to suggest trachoma. The associated symptoms and an examination of the mouth will confirm the diagnosis of keratoconjunctivitis sicca. While dryness of the conjunctiva may be extreme in trachoma, scarring of the tarsus and pannus will differentiate these cases from keratoconjunctivitis sicca, in which condition such changes do not occur.

4. *Ocular Pemphigus.* The extensive scarring seen in this condition will distinguish it from keratoconjunctivitis sicca. In pemphigus, however, lacrimal deficiency, due to obliteration of the secretory ducts, may be extreme.

5. *Superficial Punctate Keratitis and Mild Forms of Epithelial Dystrophy.*—In these conditions the corneal lesions are superficial and may vary enough to create a certain resemblance to keratoconjunctivitis sicca (16). However, the history of onset and the symptoms are different. Slit lamp examination and repeated Schirmer tests will usually establish the diagnosis.

6. *Senile Atrophy of the Lacrimal Glands.*—This condition is likely to produce keratoconjunctivitis sicca, and, as the treatment in both instances is the same, the diagnostic point need not be stressed (10).

When swelling of the parotid glands is present, the diagnostic problem is more complicated. Among the diseases to be differentiated are the following:

7. *Mumps.*—In Case I this diagnosis was made before Sjögren's disease was suspected. The history and subsequent course make the differentiation simple.

8. *Calculus in Stensen's Duct.*—This is readily ruled out by the absence of associated symptoms and by roentgenography.

9. *Tularemia.*—Here the lesions of the eyes and the mouth and the systemic signs differ from those of keratoconjunctivitis sicca. The history and agglutination tests should establish the diagnosis.

10. *Parinaud's Ocular-Glandular Syndrome.*—The history and the appearance of the two conditions are very dissimilar, and lacrimation is normal in persons suffering from Parinaud's conjunctivitis.

FIG. 2. THE SCHIRMER TEST FOR MEASUREMENT OF THE LACRIMAL SECRETION
Note the strips of filter paper, 5 mm. in width, with the upper end lying between the lower lid and the globe

11. *Sarcoid (Uveoparotid Fiver—Mikulicz's Disease).*—In this condition the corneal signs are absent and lacrimation is normal. In the Sjögren syndrome there is no iritis or leukemia and the lacrimal glands do not swell.

MEASUREMENT OF LACRIMAL SECRETION

Deficiency of lacrimal secretion is not always evident on general inspection. The amount of lacrimal secretion can be measured by a simple test devised by Schirmer (17). Strips of filter paper 5 mm. in

width and 35 mm. in length are used. One end, slightly bent, is placed in the lower cul-de-sac, at the inner angle near the punctum, and the rest of the strip is allowed to protrude between the lids (Fig. 2). When lacrimation is normal, the strip rapidly becomes moist and the moisture is measured in millimeters from the lid margin, in from 1 to 5 minutes. In our experience, the normal eye will moisten the strip in from $1\frac{1}{2}$ to 3 minutes. Less than 10 mm. in 5 minutes indicates slight diminution and under 5 mm. considerable diminution in tear flow. In patients with no lacrimation only the part of the strip in contact with the conjunctiva shows any moisture. As the many varieties of filter paper vary in their capacity to absorb fluid, each lot used should be standardized by testing beforehand on normal persons. Thin paper of a fairly smooth, firm texture is the most suitable.

The test is not entirely satisfactory, but is the best we have at present. With a little experience in evaluating the results there should be no great difficulty in determining the presence of diminished lacrimal secretion.

TREATMENT

Attempts have been made to increase glandular secretion by the use of parasympathomimetic agents. Pilocarpine, in doses of $\frac{1}{7}$ to $\frac{1}{5}$ grain, two or three times daily, caused some improvement of symptoms in one of Gifford's (16) patients. Prostigmine has been used recently. In one of our patients it caused disturbing general symptoms and no increase in lacrimal secretion. Bellows (16) compared the rate of tear flow, as shown by repeated Schirmer tests, before and after one subcutaneous injection of prostigmine hydrobromide in thirteen patients, and then after oral use of the drug for one week in five patients. The response varied after both types of administration but was quite definite in a number of cases. Other forms of systemic treatment believed to be of some value in isolated instances are the use of thyroid extract in patients with low metabolism; estrogenic extract in women who have reached the menopause; vitamins where there is a history of dietary deficiency; and liver, iron and arsenic for patients with anemia.

Local applications to the eye to stimulate lacrimation are without effect. Fibrolysin, sodium salicylate, and egg albumen have been tried. Atropine (to increase the lysozyme concentration of the tears),

physostigmine (because the symptoms resemble atropine poisoning), and acetylcholine have been advocated (10). Liquid paraffin and other oily preparations probably prevent moisture from coming in contact with the epithelium. Local exposure to roentgen-rays and radium are harmful. Contact glasses are irritating and poorly borne.

Patients with lacrimal deficiency but no corneal lesion seem, as a rule, to obtain relief from the symptoms of irritation by the use of a substitute for tears. We have found the use of gelatin and Locke's solution as proposed by Rucker very satisfactory, provided a preservative is added to prevent bacterial growth. A formula for the solution, recommended by Gifford, is as follows:

Gelatin	0.3 gram
Chloretone	0.3 gram
Locke's solution	30.0 cc.

Locke's solution is made as follows:

Sodium chloride	0.900 gram
Potassium chloride	0.024 gram
Calcium chloride	0.042 gram
Glucose	0.100 gram
Sodium bicarbonate	0.020 gram
Distilled water	100.00 cc.

Rapid depletion of the few drops of artificial tears at each instillation greatly limits the usefulness of this method treatment. More constant application is possible by means of an artificial lubricating system attached to the patient's spectacle frame (Fig. 3). This consists of a central chamber capable of holding 2 cc. of fluid, with two small tubes of plastic material, connected at its base. The tubes, directed backward, have cotton wicks at their tips to make contact with the inner canthi and to regulate the flow of artificial tear fluid.

The most satisfactory local treatment is occlusion of the puncta and canaliculi as was suggested by Beetham (18). It should be remembered, however, that while closing the canaliculi is a simple matter, keeping them closed is not easy. Any procedure less than complete destruction of the canaliculi will almost certainly prove temporary in effect. Merely sealing the puncta is of no value except as a temporary diagnostic measure. Furthermore, closure of all four canaliculi is necessary.

FIG. 3. FRONT VIEW OF AN ARTIFICIAL TEAR DROPPER

Note the central chamber built into the nose bridge of the patient's spectacles and the two small tubes with cotton wicks, leading backward towards the inner canthi.

FIG. 4. SIDE VIEW OF AN ARTIFICIAL TEAR DROPPER

Surgical removal of the canaliculi was suggested by Verhoeff (19). They can be closed very simply by galvanocautery of diathermy cauterization. A weak diathermy current, 40 to 60 milliamperes, for 20 to 30 seconds, or in our experience, until blanching of the tissues about the canal occurs, is usually adequate. The needle should be insulated to within a few millimeters of the tip, to prevent dissipation of the current at the punctum and to insure adequate desiccation of the lining epithelium at the inner end of the canal. It is usually necessary to dilate the punctum and canal slightly before introducing the diathermy needle. Too little exposure will be followed by recanalization of the canaliculus, whereas too active treatment might produce a disfiguring widening of the enteral commissure. Properly carried out, the treatment will usually result in prompt and permanent relief from the ocular symptoms.

CASE REPORTS

A total of seven patients with Sjögren's syndrome have been seen at the Wilmer Ophthalmological Institute in the last five years. The records of three of these who were seen and treated by the author are reported.

Case 1. H. H., a single woman, aged 28 years, was first seen in the Wilmer Institute dispensary on December 6, 1934. She stated that the eyes had been stinging and had been discharging a thick sticky secretion for over ten months. For years she had had great discomfort from dryness of the mouth and throat and in the morning both would contain actual crusts which could be removed digitally. For two years she had had a bleeding ulcer of the left nostril which had been treated at intervals by cauterization.

At fourteen years she had panhysterectomy, supposedly for tuberculosis. Reports on the pathological findings are not available. She had pneumonia in infancy and erythema nodosa at eighteen years of age.

Examination of the eyes disclosed extreme congestion of the palpebral conjunctivae. The corneas were clear, and the vision was 20/30 in each eye. Bacteria examination revealed the presence of normal flora. A diagnosis of chronic conjunctivitis was made. Treatment for this was instituted and she was referred to other departments for study.

On general medical examination the patient was found to be moderately obese with chronic rheumatoid arthritis, and erythema of the skin over the chest and on the fingers of the left hand. The mucous membranes of the tongue, mouth and pharynx appeared dry. The temperature, pulse rate, and respirations were

normal. The basal metabolic rate was plus 4. X-ray examination of the chest was negative. The serological test for syphilis was negative, and the blood picture was normal. Examination in the protein clinic was reported as showing moderate sensitivity to tuberculin but no allergic disease. She gave a positive reaction to 0.01 mgm. of tuberculin (O.T.) but had no reaction to any of the pollens.

Nose and throat examination showed enlargement of the upper anterior cervical glands, dryness of the mucous membranes of the tongue and pharynx, and an ulcerated area just within the vestibule of the left nostril. Roentgenograms of the sinuses showed some clouding of the left ethmoids and antrum.

On dental examination many teeth were seen to be missing and there were many carious and non-vital teeth with evidence of periapical infection. There were also calcareous deposits, causing gingivitis.

Gynecological examination revealed absence of all the pelvic organs. There was mild chronic cystitis, but guinea pig inoculations for tuberculosis were negative.

In December 1938, the left parotid gland became enlarged and moderately tender. This condition lasted for several weeks, then subsided without complications. There was a recurrence on both sides about a year later. In spite of local applications and tuberculin therapy the ocular symptoms became steadily worse. By 1940 the eyes had developed extreme photophobia. Examination at this time showed much conjunctival thickening and congestion, irregular staining of the corneas with fluorescein and many mucous and epithelial filaments adherent to both corneas. The vision was reduced to 20/70 in each eye. By the Schirmer test, lacrimation was found to be greatly diminished with moistening of only 2 mm. in each eye. A diagnosis of keratoconjunctivitis sicca was made. Following closure of the lacrimal canals there was prompt relief from the distressing ocular symptoms, rapid clearing of the corneas and improvement in the vision.

Case 2. A. C., a widow, aged 60 years, was first seen on March 5, 1941. She complained that for one year the mouth had been dry and for three weeks the eyes had been irritated and stinging.

The personal history reported what she called "poor digestion and loss of appetite" for the last two to three years. Her menstrual flow stopped at the age of forty-eight years.

On examination fissures were seen at the corners of the mouth and ulcerated yellowish areas on the gums and hard palate. The mouth and throat were dry. The tongue was dry and smooth with a purplish red color. There were areas of acne rosacea on the face. Many of the joints, particularly of the hands, showed signs of hypertrophic arthritis.

The laboratory reports were as follows: The urine was negative; the Wassermann test was negative; the blood nonprotein nitrogen, sugar, uric acid, and serum proteins were normal. The hemoglobin was 11 gm. per cc. (79 per cent); the red blood corpuscles were 4,590,000; and the white corpuscles, 8,250; there was slight achromia and anisocytosis. The basal metabolic rate was plus 6.

The eyes showed moderate conjunctival congestion and some stringy discharge.

On the lower third of each cornea were a few superfical grayish spots and many mucoid filaments. Vision in the right eye was 20/30; that in the left, 20/50. By the Schirmer test, lacrimation was moderately diminished, with moistening of 9–10 mm. after five minutes in each eye. The conjunctival flora was normal.

On September 4, 1941, she was admitted to the medical ward with pneumonia. She was thought also to have avitaminosis.

By October, 1941, the ocular symptoms were more pronounced than before and typical epithelial filaments were seen on the corneas. The Schirmer test showed moistening of only 4 mm. in five minutes in each eye. Both parotid glands were enlarged and slightly tender. There was swelling of both hands from acute arthritis of the carpal and wrist joints. On October 20, 1941, all four puncta and canaliculi were occluded permanently. Improvement in the ocular symptoms was immediate. When seen a year later the eyes were comfortable and adequately moist and the vision was 20/20 in each eye.

Case 3. B. B., a housewife, aged 30 years, was admitted to the medical service of Dr. Wainwright on September 13, 1942. She complained of pain and deformity of the knees and fingers for eight years. For two years the eyes had been irritated and extremely sensitive to light. On crying or laughing no tears formed. The vision was failing.

In 1936, following an attack of erythema multiforme, she was tested for bacterial allergy, and vaccines for two organisms as well as autogenous vaccines were used, all with little or no effect on the course of the arthritic symptoms.

Physical examination disclosed extensive active rheumatoid arthritis. The skin and hair were almost pigment free. There was bilateral pansinusitis. She was edentulous. The mouth was dry, and the tongue had a dry, smooth, glistening appearance. The skin was dry.

Vision in the right eye was 20/70, that in the left, 20/50. There was intense photophobia and blepharospasm. The conjunctivae were dry and congested. There was superficial haziness of the corneas and irregular staining with fluorescein. Many epithelial and mucous filaments were seen on the lower third of the corneas. There was great deficiency of lacrimal secretion with moistening of less than 2 mm. on the Schirmer test after five minutes. The conjunctival flora was normal.

Laboratory reports were as follows: The hemoglobin was 13.3 gm. per 100 cc. (92 per cent); the red blood corpuscles were 4,200,000, the white corpuscles, 5,850; there was slight polychromatophylia, pronounced anisocytosis and slight poikilocytosis; the eosinophiles were 5 per cent. The blood nonprotein nitrogen, sugar, uric acid and serum proteins were normal. Gastric analysis showed no free acid one hour after taking alcohol. The sedimentation rate corrected to 37 mm. The serological test for syphilis was negative. Roentgenograms of the sinuses showed chronic pansinusitis.

On October 15, 1942, all four puncta and canaliculi were occluded permanently. Three days later the patient was free of ocular symptoms and the relief has persisted to date. When she was seen one year later there were no ocular symptoms and the vision was 20/20 in each eye.

SUMMARY

Deficient lacrimation may produce a troublesome keratoconjunctivitis. In the absence of obvious systemic disorders the true nature of the disease is not always recognized. When it is associated with xerostomia and swelling of the parotid glands (the Sjögren syndrome), the condition is easily recognized.

Three cases of the Sjögren syndrome are reported. The diagnosis and theories regarding etiology are discussed and an effective method of treating the ocular condition is described.

REFERENCES

1. Stock: Handb. d. ges. Augenheilk., 1924, **9,** Berlin.
2. Duke-Elder, W. S.: Brit. J. Ophth., 1930, **14,** 61.
3. Schöninger: Klin. Mbl. f. Augenheilk., 1924, **73,** 208.
4. Scheerer: Ber. deutsch. Ophthal. Ges., Heidelberg, S., 1928, 304.
5. Betsch, A.: Klin. Mbl. f. Augenheilk., 1928, **80,** 618.
6. Isakowitz: Klin. Mbl. f. Augenheilk., 1928, **81,** 85.
7. Sjögren, H.: (a) Acta Ophth., 1933, **11** supp., 1. (b) Acta Ophth., 1938, **16,** 70. (c) A New Conception of Keratoconjunctivitis Sicca. Translation into English by J. Bruce Hamilton with a Foreword and Appendix. Sydney, Australasian Medical Publishing Company, Ltd., 1943.
8. Albrich, K.: Arch. of Ophth., 1928, **121,** 402.
9. Dalsgaard-Nielsen, E. and T.: Ugesk f. laeger, 1937, **99,** 219.
10. Grosz, S. von: Klin Mbl. f. Augenh., 1936, **97,** 472.
11. Bruce, G. M.: Tr. Amer. Ophth. Soc., 1940, **38,** 149.
12. Krasso, I.: Ztschr. f. Augenh., 1930, **71,** 1.
13. Lisch, K.: Arch. f. Augenh., 1937, **110,** 357.
14. Knapp, P.: Klin. Mbl. f. Augenh., 1929, **82,** 241.
15. Bassalino, G.: Boll. d'ocul., 1936, **15,** 1193.
16. Gifford, S. R., Puntenney, T., and Bellows, T. G.: Tr. Amer. Ophth. Soc., 1942, **41,** 80.
17. Schirmer, O.: Arch. of Ophth., 1903, **56,** 197.
18. Beetham, W. P.: Tr. Amer. Ophth. Soc., 1935, **33,** 413.
19. Verhoeff, F. H.: Amer. J. Ophth., 1925, **8,** 273.
20. Yudkin, A. M., and Lambert, R. A.: Proc. Soc., Exper. Biol. and Med., 1922, **19,** 375.

FURTHER OBSERVATIONS ON THE SELF-REGULATORY DIETARY SELECTIONS OF RATS MADE DIABETIC BY PANCREATECTOMY[1]

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Numerous instances have been offered to demonstrate the reliability of the rat's appetite as a guide to its dietary needs (1). It was shown that appetite may be used as a quick and accurate indicator of the factors involved in endocrinological and nutritional disturbances which might otherwise be discovered only after prolonged or chance clinical observations. This indicator has now been used for a second study of the factors involved in diabetes produced by sub-total removal of the pancreas in rats.

The previous study showed that pancreatectomized rats which for months on a regular stock diet had manifested all the signs of diabetes, —namely polydipsia, polyphagia, loss of weight, hyperglycemia,—lost these signs when permitted to select their own diets from an assortment of 10 substances in separate containers: one representative of each of the most important food elements (casein, olive oil, sucrose, sodium chloride, dibasic sodium phosphate, magnesium chloride, potassium chloride, calcium lactate, cod liver oil, and either dried Baker's yeast or dried liver powder) (2). These rats selected high amounts of fat, 56 per cent on the average, low amounts of carbohydrate, 19 per cent, and large amounts of yeast (about twice as much as the average for normal rats kept on the same diet). The protein intake increased in some rats, decreased in others. When the rats were returned to the stock diet and were thus forced to take the various ingredients in fixed amounts all of the symptoms of diabetes reappeared.

In further experiments of the previous study rats were allowed to select their diet from the same ten substances for a month or longer before they were pancreatectomized. After pancreatectomy these

[1] Carried out under a grant from the Committee on Research in Endocrinology.

[2] Denison Prize Scholar 1939–1941: now Captain, Medical Corps, U.S.A. These experiments were carried out during the three years of the scholarship.

rats did not show any symptoms of diabetes so long as they remained on this self-selection diet. However, immediately after they were placed on the stock diet, and thus forced to take the various ingredients in fixed proportions, they showed all of the signs of diabetes. These rats took more fat (68 per cent as compared to 38 per cent) and less carbohydrate (9 as compared to 36 per cent) than before. They showed irregular changes in appetite for the protein casein and for yeast or liver powder.

Although from these results it could be definitely concluded that pancreatectomized rats have an increased appetite and need for fat and decreased appetite and need for carbohydrate, no conclusions could be drawn regarding their appetite and need for either protein or the sources of the vitamin B complex, since some of the rats took more protein, others less; similarly with yeast or liver powder. The lack of consistency in regard to the appetite shown for the yeast may have depended at least in part on the presence in this substance of numerous ingredients, not only of the various members of the vitamin B complex, but particularly of carbohydrate and protein. Thus, although the rats may have wanted more of the components of the vitamin B complex or more protein, they may have taken less of the yeast on account of its high carbohydrate content.

In the experiments described below we have attempted to eliminate some of these complications and to obtain a more definite answer regarding the appetite and need for protein and for the various components of the vitamin B complex.In the assortment of substances offered for choice the yeast or liver powder was omitted and replaced by solutions of 6 crystalline components of the vitamin B complex: thiamine hydrochloride, riboflavin, nicotinic acid, pyridoxine, calcium pantothenate and choline chloride. Thus the vitamin-free casein constituted the sole source of protein, the dextrose (in place of sucrose) the sole source of carbohydrate, and olive oil and cod liver oil the only sources of fat, and the 6 solutions the only sources of the vitamin B complex. From the results of previous experiments we know th t on the selections made from this assortment of substances some rats will show normal growth curves but most rats will approximately maintain their weight, and that growth varies directly with the protein intake (3). The fact that not all the rats show normal growth curves probably

indicates that the assortment lacks some needed substance, perhaps some other member of the vitamin B complex, or vitamin E, vitamin D, iodine, iron, copper, cobalt, etc. It is of special interest that on this self-selection diet all unoperated rats without exception have manifested a great appetite for carbohydrate and a very small appetite for fat when offered the six vitamin B components listed above.

In the present experiments the rats were kept on the self-selection diet with the crystalline vitamin B components for at least 40 days before pancreatectomy. Postoperatively they were observed on the self-selection diet for at least 40 days and in some instances for 130 days before they were placed on the stock diet. Thus, except for the slightly reduced rate of growth of these rats and their great appetite for carbohydrate and small appetite for fat, the conditions of these experiments were essentially the same as those present in the second part of our previous experiments.

METHODS

The rats were kept separately in self-selection cages with two food cups containing casein (Labco—fat and water soluble vitamin-free) and dextrose C.P. and with 14 graduated inverted 100 or 30 cc. bottles which contained the following substances:

Fat

1. Olive oil

Minerals

2. Sodium chloride 3%
3. Dibasic sodium phosphate 4%
4. Potassium chloride 1%
5. Magnesium chloride 0.5%
6. Calcium lactate 2%

Vitamin A and D

7. Cod liver oil

Vitamin B Complex

8. Thiamine hydrochloride 0.02%
9. Riboflavin 0.00125%
10. Nicotinic acid 0.1%
11. Pyridoxine 0.02%
12. Calcium pantothenate 0.01%
13. Choline chloride 0.5%
14. Tap water

The concentrations of the mineral and vitamin solutions were determined on a purely empirical basis. We attempted to use concentrations at which the daily intake would be sufficiently high to be measured easily (that is, 3–7 cc. of each solution) but still not so high as to burden the animal with an excessively large water intake. All solutions were made with distilled water. Evaporation ranged from 0.5 to 1 cc. per day.

Records were made of the intake of each substance daily including Sundays; activity and vaginal smear records were made daily also. This meant that 16 readings were made on each rat each day. The rats were weighed weekly. As in the previous experiments, a separate chart for each animal showed the intake of each of the different substances, as well as of the running activity, vaginal smears and body weight. All the bottles were cleaned and refilled at least twice each week; the pyridoxine, riboflavin, and choline chloride solutions were changed each day. Blood sugar determinations were not made because maneuvers involved in blood-letting often produce profound disturbances on the dietary selections and activity.

The 8 female rats used in this experiment had at least maintained their weight on the self-selection diet for 40 or more days preoperatively. Their ages at operation averaged 131 days, varying from 111 to 150. After pancreatectomy they were kept on the self-selection diet at least another 40 days, then returned to the regular stock diet,[3] and later placed on a variety of experimental diets based on the knowledge obtained from the self-selection studies.

The operative technique used for the removal of the pancreas was essentially the same as that used in our previous experiments (2). It was modified from that first described by Shapiro and Pincus (4). The drawing in Figure 1 shows the pancreas and its attachments to the stomach, spleen, intestines, and bile duct. Figure 2 shows the four main stages of the operation. Through a midline incision about 1½ inches long beginning at the sternum, the spleen and attached pancreatic tissue were located, and held in the position shown in stage 1. By gentle rubbing between the thumb and forefinger of the left hand, or by suction through a well annealed glass cannula under negative pressure from a water pump, the pancreatic tissue was freed from the pancreaticoduodenal vessels. The spleen was then pulled up through the incision, as is shown in stage 2. By means of a small straight pair of forceps the pancreatic tissue was cleaned away from the colon and its vessels. The colon and spleen were replaced in the abdominal cavity and the duodenum was brought into the position shown in

[3] Graham flour 72.5%, casein 10.0%, skim milk powder 10.0%, butter 5.0%, sodium chloride 1.0%, calcium carbonate 1.5%. This diet contains 59.8% carbohydrate, 14.9% fat, and 25.3% protein.

stage 3. The pancreatic tissue was then removed from the duodenum and its vessels, partly by rubbing and rolling between the thumb and forefinger of the left hand, partly by aspiration. In this way all of the remaining pancreatic tissue could be removed. However, in these experiments some of the tissue between the bile duct and the duodenum was deliberately left intact since we found very poor survival rates after complete removal of pancreatic tissue (5). Furthermore, com-

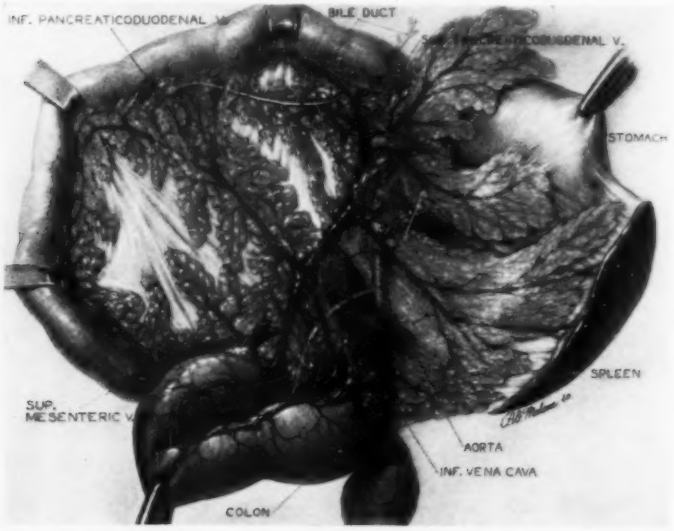

FIG. 1. PANCREAS OF THE RAT. DRAWING SHOWING THE ENTIRE GLAND AND ITS ATTACHMENT TO THE STOMACH, SPLEEN, COLON AND DUODENUM

pletely pancreatectomized animals do not show either polydipsia or polyphagia although they show an increased blood sugar. Thus, in the present experiments all of the operations were partial rather than total pancreatectomies.

The operation was performed under ether anesthesia. Care was taken to expose only a small portion of the intestines to the air at any one time and to keep the viscera well moistened with warm saline solution. For 10 to 20 hours preoperatively the rats were given access only to a 40 per cent solution of dextrose. Postoperatively the animals

were returned at once to the activity cages and the full self-selection diet.

This procedure has produced diabetes in approximately 80 per cent of our rats. At present we do not know why some of the rats do not develop diabetes, though the explanation may depend on variations in the relative amounts of internal and external secretions that come from the remaining minute fragments of pancreatic tissue.

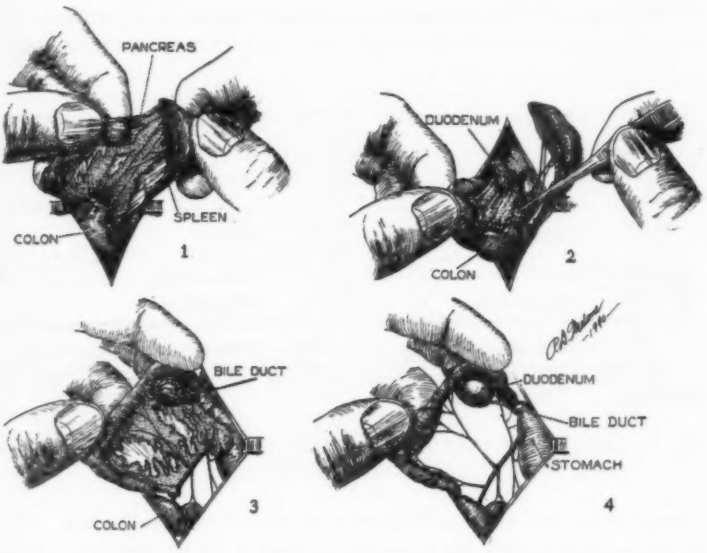

FIG. 2. FOUR STAGES OF THE OPERATION USED IN REMOVING THE PANCREAS

In these experiments, as in our previous ones in which the rats were pancreatectomized while on the self-selection diet, it was not possible to determine, so long as the rats remained on the self-selection diet, whether they actually suffered from diabetes. This did not become apparent until the animals were placed on the stock diet. Then the appearance of a marked polyphagia or polydipsia or both was taken as indication that the rats suffered from diabetes. Of the 8 rats used in these experiments 5 showed both a marked polyphagia and polydipsia when placed on the stock diet; one showed a polyphagia but no polydipsia, two showed polydipsia but no polyphagia.

RESULTS

Carbohydrate, Fat and Protein Appetite before and after Pancreatectomy

Figure 3 shows records of the dextrose, casein, cod-liver oil and olive oil intakes of two of the rats. Rat #6 (Figure 3A) was started on the self-selection diet at an age of 83 days. From then until it reached the age of 104 days, when it was pancreatectomized, its dietary selections remained fairly constant. It took large amounts of dextrose, 12–14 grams per day, moderate amounts of casein, 2–3 grams per day, and almost no cod-liver oil or olive oil. For 18 days after pancreatec-

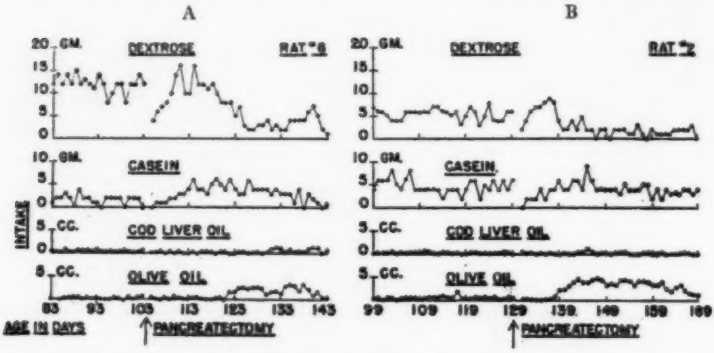

FIG. 3. DIETARY SELECTIONS MADE BY RATS #6 AND #2 BEFORE AND AFTER PANCREATECTOMY

tomy it continued to take high amounts of dextrose and no fat. Then its fat and carbohydrate appetites showed a sharp reversal. At the end of the third 10-day-period it took twice as much, measured in calories, of the two fats as of the carbohydrate. The casein intake increased almost at once after pancreatectomy and after 10–20 days was 2 to 3 times as high as before. After pancreatectomy rat #2 (Figure 3B) took considerably larger amounts of olive oil than of dextrose. Its casein intake was high both before and after pancreatectomy.

Figure 4 shows the records of two other animals. Rat #8 (Figure 4A) continued to take very high amounts of dextrose for over 20 days after pancreatectomy, then within a few days stopped taking it almost altogether. It took much larger amounts of the protein than did rats

#6 and #2, finally reaching a casein intake close to 9 grams per day, which is unusually high. During the last two 10-day-periods shown in this record the protein constituted over 90 per cent of the total food intake. During the first 50 days postoperatively this rat showed no

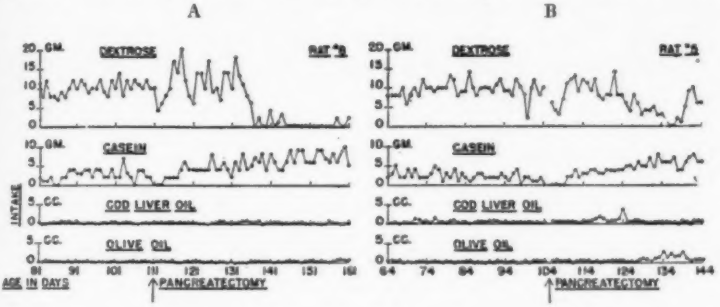

FIG. 4. DIETARY SELECTIONS MADE BY RATS #8 AND #5 BEFORE AND AFTER PANCREATECTOMY

TABLE I

Average Daily Intake in Calories per Kilogram Body Weight

(Last 20 days before pancreatectomy and last 20 days postoperatively on self-selection diet)

RAT NO.	DEXTROSE		COD LIVER OIL AND OLIVE OIL		CASEIN	
	Before	After	Before	After	Before	After
1	181.3	51.2	47.5	185.3	37.0	60.4
2	155.4	42.0	55.4	194.9	117.5	100.8
3	100.0	77.6	55.8	120.8	47.4	53.5
4	178.2	91.6	62.8	85.6	37.9	43.4
5	238.0	125.4	37.3	133.7	53.1	159.4
6	265.9	71.6	25.4	112.3	40.4	61.0
7	210.9	125.6	43.0	37.9	75.8	99.0
8	272.3	80.2	18.3	29.0	73.3	149.6
Average.....	200.3	83.2	43.2	112.4	60.3	90.9

increase in fat consumption, later it also showed the usual large increase in fat intake. Rat #5 showed a similar record with an almost immediate increase in casein appetite after pancreatectomy.

Table I gives the average daily intake of dextrose, cod-liver oil and olive oil, and casein in calories per kilogram body weight for the last

20 days before pancreatectomy and for the last 20 days postoperatively on the self-selection diet. The average daily intake of dextrose which represented the sole source of carbohydrate decreased from 200.3 to 83.2 calories per kilogram of body weight, all 8 rats showing a decrease. The average daily intake of cod-liver oil and olive oil which represented the only sources of fat increased from 43.2 to 112.4, 7 of the 8 rats showing an increase. The casein intake increased from 60.3 to 90.9, 7 of the 8 rats showing an increase. The casein intake of Rat #2 which was slightly lower than the preoperative average was still well above the average for the 8 rats.

TABLE II

Caloric Percentages

(Last 20 days before pancreatectomy and last 20 days after pancreatectomy on self-selection diet)

RAT NO.	CARBOHYDRATE		FAT		PROTEIN	
	Before	After	Before	After	Before	After
1	68.2	17.3	17.9	62.4	13.9	20.3
2	47.3	12.4	16.9	57.7	35.8	29.9
3	49.2	30.8	27.5	48.0	23.3	21.2
4	63.9	41.5	22.5	38.8	13.6	19.7
5	72.5	30.0	11.4	31.9	16.1	38.1
6	80.2	29.2	7.6	45.9	12.2	24.9
7	64.0	47.9	13.0	14.4	23.0	37.7
8	74.9	31.0	5.0	11.2	20.1	57.8
Average.....	65.0	30.0	15.2	38.8	19.8	31.2

Table II shows the average daily intake of carbohydrate, fat, and protein in caloric percentages for the 8 rats. On the average the caloric intake of carbohydrate decreased from 65.0 to 30.0 per cent; fat intake increased from 15.2 to 38.8 per cent; protein intake increased from 19.8 to 31.2 per cent.

Table III gives the average daily intake in milligrams of the six components of the vitamin B complex for the last 20 days before pancreatectomy, and for the first and last 20 day postoperative periods respectively. In this table no deductions have been made for evaporation, which actually varied from 0.4 to 1.0 cc. daily. Thus the values

given here are definitely higher than the actual consumption of the animals. During the first 20 day postoperative period the intake of all

TABLE III

Vitamins—Average Daily Intakes and Ranges of Variation

Vitamins in Mg.

VITAMIN	SOLUTION	LAST 20 DAYS PREOPERATIVELY	FIRST 20 DAYS POSTOPERATIVELY	LAST 20 DAYS POSTOPERATIVELY
	per cent			
Thiamine Chloride.....	0.02	0.2 (0.1– 0.3)	0.4 (0.2– 1.2)	0.6 (0.2– 2.7)
Riboflavin.....	0.00125	0.1 (10.0– 0.2)	0.3 (0.1– 0.6)	0.2 (0.1– 0.3)
Nicotinic Acid.....	0.1	2.0 (0.7– 5.5)	5.1 (1.3– 8.5)	2.0 (0.8– 5.2)
Pyridoxine.....	0.02	0.4 (0.2– 1.2)	1.3 (0.3– 4.3)	1.0 (0.2– 2.6)
Pantothenic Acid.....	0.01	0.3 (0.1– 1.3)	1.1 (0.4– 2.1)	0.7 (0.1– 1.4)
Choline Chloride.....	0.5	10.0 (4.5–15.5)	20.0 (8.0–46.0)	13.0 (4.0–32.0)

TABLE IV

Minerals—Average Daily Intakes and Ranges of Variation

Minerals in Mg.

MINERAL	SOLUTIONS	LAST 20 DAYS PREOPERATIVELY	LAST 20 DAYS POSTOPERATIVELY
	per cent		
Sodium Chloride.....	3	204.0 (57.0–381.0)	135.0 (51.0–372.0)
Sodium Phosphate.....	4	204.0 (40.0–348.0)	168.0 (64.0–420.0)
Potassium Chloride.....	1	35.0 (13.0– 50.0)	31.0 (14.0– 53.0)
Magnesium Chloride.....	0.5	19.5 (7.0– 38.5)	27.0 (7.0–124.5)
Calcium Lactate.....	2	66.0 (22.0–138.0)	100.0 (82.0–142.0)

the vitamins manifested a 2-to-3 fold increase. Thus, the average daily intake of thiamine hydrochloride increased from 0.2 to 0.4 mg.; riboflavin from 0.1 to 0.3 mg. During the last 20 day postoperative

period the thiamine hydrochloride, riboflavin, pyridoxine, and pantothenic acid intakes were still definitely above their preoperative levels while those of nicotinic acid and choline chloride no longer showed a significant increase.

Compared to the appetite of the 8 rats for carbohydrate, fat and protein, the appetites for the 6 members of the vitamin B complex showed much greater variation and individual differences. For this reason and on account of the variations which might be due to differences in evaporation we do not feel at the present time that the changes indicated in vitamin B appetites have more than a suggestive value.

Mineral Appetite. Table IV gives the average daily intake of the 5 mineral solutions in milligrams for the last 20 days preoperatively and for the 20 to 40 day postoperative period. The averages for all of the rats as well as for the individual rats failed to reveal any consistent changes in appetite. Essentially the same observations were made in the previous experiments in which yeast and liver powder were used in the self-selection diet.

Effects Produced by the Dietary Selections on Water and Food Intake, Activity, and Body Weight

Water Intake. Figure 5A gives the total fluid intake record (water from the 5 mineral solutions, the 6 vitamin solutions, added to that from the tap water bottle) in 10 day averages for Rat #6 whose record of dietary selections was presented in Figure 3A. For the first two 10 day periods before pancreatectomy the daily intake averaged 45 cc.; for the two 10 day periods after pancreatectomy it increased to 74.3 and 103 cc. respectively. These high levels of water intake coincided with the periods of high dextrose intake. For the last two 10 day periods on the self-selection diet the intake decreased to an average of 40 cc. which was slightly below that before pancreatectomy. Immediately after the rat was changed from the self-selection to the stock diet the total fluid intake started to increase at a rapid rate, averaging 85 cc. at the end of 40 days. Figure 5B gives the average daily water intake record in 10 day periods for Rat #2 whose record of dietary selections was presented in Figure 3B. During the last three 10 day periods before pancreatectomy the intake averaged about 30 cc. After pancreatectomy it increased at once to a level between 50 and 60 cc. at

which it was maintained fairly steadily so long as the rat remained on the self-selection diet; when this was replaced by the stock diet the total fluid intake increased sharply, finally reaching an average of 105 cc. per day.

The first three columns of Table V give the average daily total fluid intake records for the 8 different animals, showing an increase from 30 cc. for the last 20 days before pancreatectomy to 51 cc. for the

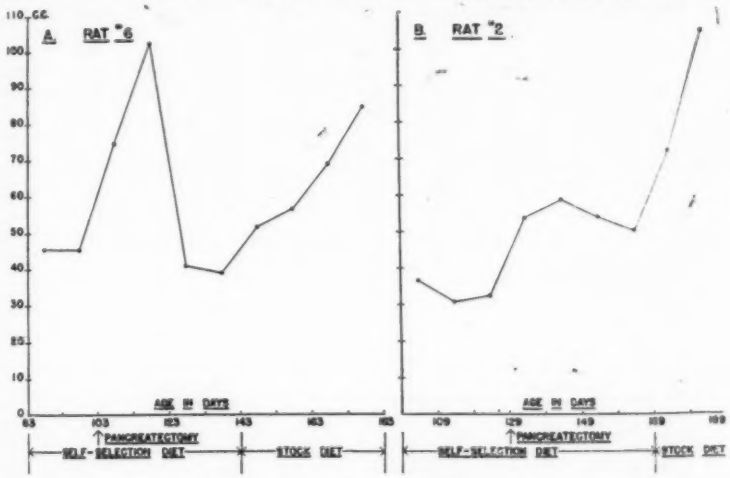

FIG. 5. AVERAGE DAILY TOTAL WATER INTAKE OF RATS #6 AND #2 BEFORE AND AFTER PANCREATECTOMY ON SELF-SELECTION DIET AND AFTER BEING PLACED ON THE STOCK DIET

last 20 days on the self-selection diet postoperatively; and to 76 cc. for the last 10 days on the stock diet. Six of the 8 rats showed the increase postoperatively on the self-selection diet and all 8 showed the increase on the stock diet.

It must be noted that in these experiments the rats could satisfy their thirst from any or all of 12 different bottles: 6 filled with the vitamin solutions, 5 with the mineral solutions, and one with tap water. Figure 6 shows curves for the average daily total fluid intake from the vitamin solutions, mineral solutions, and for the tap water. For water lost from evaporation 1 cc. was arbitrarily deducted from each bottle.

TABLE V

RAT NO.	AVERAGE DAILY TOTAL WATER INTAKE (CC.)			AVERAGE DAILY TOTAL FOOD INTAKE (CALORIES PER KILOGRAM BODY WEIGHT)			BODY WEIGHT (GRAMS)		
	Self-selection diet			Self-selection diet					
	Last 20 days before pancreatectomy	Last 20 days of postoperative treatment	Stock diet, last 10 days	Last 20 days before pancreatectomy	Last 20 days of postoperative treatment	Stock diet, last 10 days	At operation	At end of period on self-selection diet	At end of period on stock diet
1	31	21	28	266	297	349	165	180	193
2	22	40	97	328	338	529	135	147	163
3	21	34	78	203	252	360	155	160	185
4	31	50	59	279	221	327	190	178	205
5	42	118	135	328	419	494	175	167	175
6	35	28	76	332	245	356	185	200	217
7	26	46	62	330	263	214	155	163	167
8	29	67	72	364	259	329	160	175	175
Average ...	30	51	76	304	287	370	165	171	185

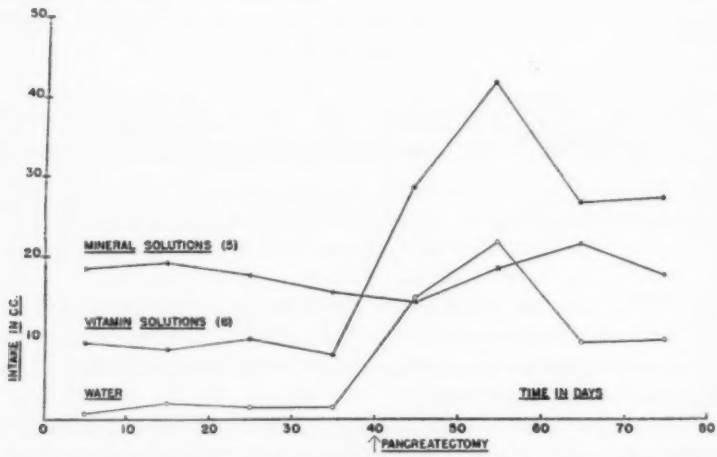

FIG. 6. AVERAGE DAILY FLUID INTAKE FOR 8 RATS FROM 5 MINERAL SOLUTIONS, 6 VITAMIN SOLUTIONS AND TAP WATER

Before pancreatectomy the rats took high amounts of the mineral solutions, a total of 18 cc. per day on the average; approximately half as much of the vitamin solutions, 9 cc. per day on the average; and a

very small amount of the water, 1.5 cc. per day. After pancreatectomy the total intake of the mineral solutions showed only a very small increase if any at all; the total intake of the vitamin solutions showed a great increase, from 9 cc. to a peak of 41 cc., more than 4-fold increase, while the intake of tap water showed an even greater increase, from 1.5 cc. to a peak of 21.8 cc. or a 14-fold increase.

Thus it is clear that after pancreatectomy the rats had an increased thirst for water. Further, since they took more of the vitamin solu-

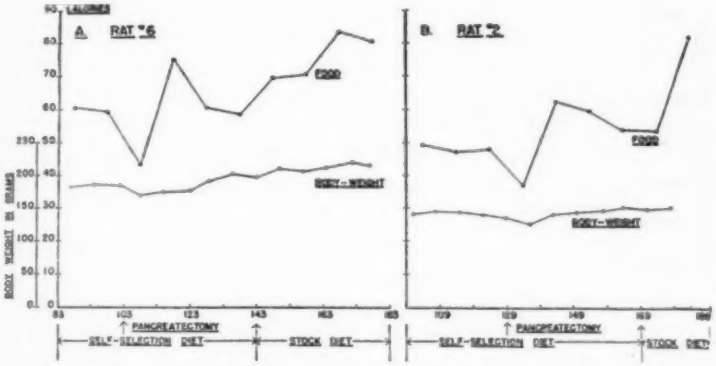

FIG. 7. AVERAGE DAILY FOOD INTAKE IN CALORIES FOR RATS 6 AND #2 BEFORE AND AFTER PANCREATECTOMY ON THE SELF-SELECTION DIET AND AFTER BEING PLACED ON THE STOCK DIET

tions, although the 5 mineral solutions and plain water were available, it can be concluded that they took more of these solutions to obtain increased amounts of the vitamins and not simply to get more water.

Food Intake. Figure 7 shows a record of the food intake in calories in 10 day averages for the rats whose records of dietary selections were presented in Figure 3. For the last two ten day periods before pancreatectomy the total food intake for Rat #6 averaged about 60 calories. There were no consistent changes in total food consumption during the first 40 days postoperatively, while the animal was still on a self-selection diet, but there was a definite increase in caloric ingestion when the rat was placed on the stock diet. Rat #2 showed similar changes in food intake.

The second part of Table V summarizes the results of these observa-

tions giving the average daily food intake in calories per kilogram body weight for each of the 8 rats. The average caloric intake decreased from 304 for the last 20 days before pancreatectomy to 287 for the

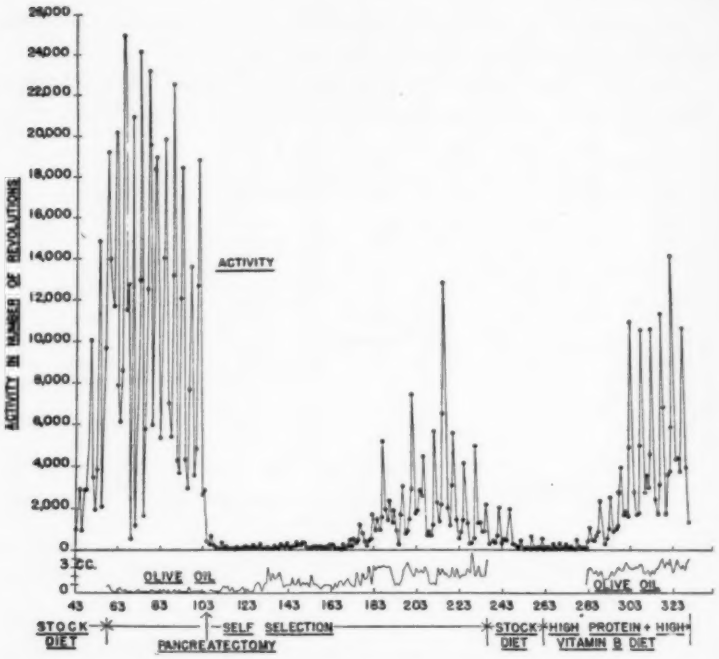

FIG. 8. DAILY RUNNING ACTIVITY AND OLIVE OIL INTAKE OF RAT #5 PANCREATECTOMIZED AT AN AGE OF 104 DAYS

This rat started on the self-selection diet at the age of 60 days and remained on it until it was 236 days of age, after that it was placed on the stock diet for 26 days, and then on a high protein and vitamin B diet. Twenty days after it started on the latter diet it was given access to olive oil in a separate container from its food.

last 20 days postoperatively on the self-selection diet, 4 showing an increase, 4 a decrease. After the rats were placed on the stock diet the intake increased sharply to 370 calories, 7 of the 8 rats showing a marked increase.

Body Weight. None of the 8 rats lost weight after pancreatectomy. Their average body weight increased from 165 grams on the day of operation to 171 grams for the last day on the self-selection diet. Thus they did not show the decrease in weight which regularly follows pancreatectomy in rats receiving the stock diet (5).

Activity. Figure 8 shows the daily running activity of one of the rats on which activity records were obtained. The ordinates give activity in number of revolutions of the drum, the abscissae age in days. The intake of olive oil on the self-selection diet is also shown. The rat was placed in the activity cage, on the stock diet, at the age of 43 days. During the 17 days that it remained on the stock diet its activity increased steadily, reaching an average near 12,000 revolutions. During the following 43 days on the self-selection diet and before pancreatectomy it remained very active and its activity showed 4 day cycles corresponding with the oestrous cycles as reflected in the vaginal smears. Immediately after pancreatectomy the rat became almost totally inactive. For the first 60 days it seldom ran more than a few hundred revolutions in any one day. Then it started to become more active again, finally attaining a level between 2 and 3 thousand revolutions per day and showing fairly regular 4 day cycles. It will be noted that the increase in running activity corresponded closely with a second sharp rise in the intake of olive oil. When, at an age of 236 days, it was placed on the stock diet it quickly became almost totally inactive again. The rest of this chart will be discussed below.

The other 5 rats gave essentially similar records though some of them remained very active throughout the self-selection period. That they should show any activity at all is remarkable in view of our previously reported observation that pancreatectomized rats kept on the stock diet remained almost totally inactive (5). In general the amount of activity appeared to parallel the intake of olive oil.

Effect of Special Fixed Diets on Diabetic Symptoms

In the above experiments it was found that diabetic symptoms either did not appear, or at least remained quite mild, so long as the pancreatectomized rats could select their own diets, but that the symptoms became very prominent as soon as the rats were given the stock diet. We were interested to determine whether after the rats had

been on the stock diet for several weeks the addition to the stock diet of high amounts of protein, high amounts of the different components of the vitamin B complex, or high amounts of fat would reduce or eliminate the diabetic symptoms.

High Protein Diet. For 26 days 4 of the rats were kept on a diet made up of the stock diet to which a large amount of casein had been added. In this diet carbohydrate constituted 36.3 per cent, fat 9.9 per cent, and protein 53.8 per cent. This diet did not reduce the food or water intake or increase the activity of any of the 4 rats. On the contrary it made the rats less active, as might have been expected from our previous experiments in which it was found that rats are less active on a high protein diet (6).

High Protein, High Vitamin B Diet. Large amounts of the different components of the vitamin B complex were added to the high protein diet and given to all 8 rats (200 mg. of thiamine hydrochloride, 200 mg. of riboflavin, 200 mg. of nicotinic acid, 200 mg. of pyridoxine, 250 mg. of calcium pantothenate, and 100 mg. of choline chloride were added to each kilo of the high protein food). Over a period of 20 days none of the rats on this diet showed any change in activity or in water intake.

High Protein, High Vitamin B, High Fat Diet. Six of the 8 rats on the high protein, high vitamin B diet were given access also to a bottle of olive oil for periods varying from 50 to 90 days. All 6 rats drank much less water than either on the immediately preceding diet or on the regular food diet. When 2 of the animals were later placed on the regular diet their water intakes again increased to a high level (from 42 to 103.0 cc. and from 62.4 to 131.0 cc. respectively) and the total caloric intakes increased to a much higher level (from 436.6 to 630.0 and from 313.1 to 482.6 respectively). When given access to olive oil all the rats on which activity records were taken became much more active. Figure 8 includes the record of one of these animals. As was pointed out above, this rat became very inactive when at the age of 236 days it was taken off the self-selection diet and placed on the stock diet, and remained inactive when placed on the high protein and high vitamin B diet. When at the age of 282 days it was given access to olive oil it took fairly large amounts (3 to 4 cc.) and almost immediately became active, and showed 4 day cycles of running ac-

tivity together with cornified cells in the vaginal smears. Its activity was still increasing at a steady rate when at the end of an 80 day period the experiment was terminated. The other 3 rats also showed an increase in activity after they were given access to olive oil.

Comparison of Changes in Appetite, Water Intake, Etc., Produced by the Yeast and Vitamin B Component Self-selection Diets

A comparison may now be made between the results obtained in the present self-selection experiments in which the pancreatectomized rats obtained their vitamin B from the solutions of 6 separate crystalline

TABLE VI

Comparison of Results Obtained in Previous Experiments in Which Rats Received the Vitamin B Components in the Form of Yeast, with Results of Present Experiments in Which the Rats Received Purified Vitamin B Components in Separate Solutions

	LAST 20 DAYS BEFORE PANCREATECTOMY		LAST 20 DAYS ON SELF-SELECTION DIET		LAST 10 DAYS ON STOCK DIET	
	Yeast	Vitamin B components	Yeast	Vitamin B components	Yeast	Vitamin B components
Average daily food intake (calories per kilogram body weight)	245	304	256	287	342	370
Average daily water intake (cc.)	29	30	29	51	51	76
Caloric percentages						
Carbohydrate	36	65	9	30		
Fat	38	15	68	39		
Protein	26	20	23	31		
Average body weight (grams)	180	165	197	171	200	185

components of the vitamin B complex, with those obtained in the previous experiments in which yeast was used as source of the vitamin B complex. Table VI compares the data of these two experiments for the last 20 days before pancreatectomy, for the last 20 days on the self-selection diet, and for the last 10 days on the stock diet. The daily food intake in calories per kilogram body weight of the yeast-fed rats increased slightly after pancreatectomy (245–256) while that of the rats offered the vitamin B components decreased slightly (304–287). Neither group of rats showed any polyphagia after pancreatec-

tomy. On the stock diet, however, the rats of both groups showed a marked polyphagia, the intake of the yeast-fed rats increasing from 256 to 342 calories, and that of the vitamin B-fed rats from 287 to 370 calories. Measured in cabric percentages the pancreatectomized rats on the vitamin B components took over three times as much carbohydrate (30 as compared to 9 per cent), about one-third more protein

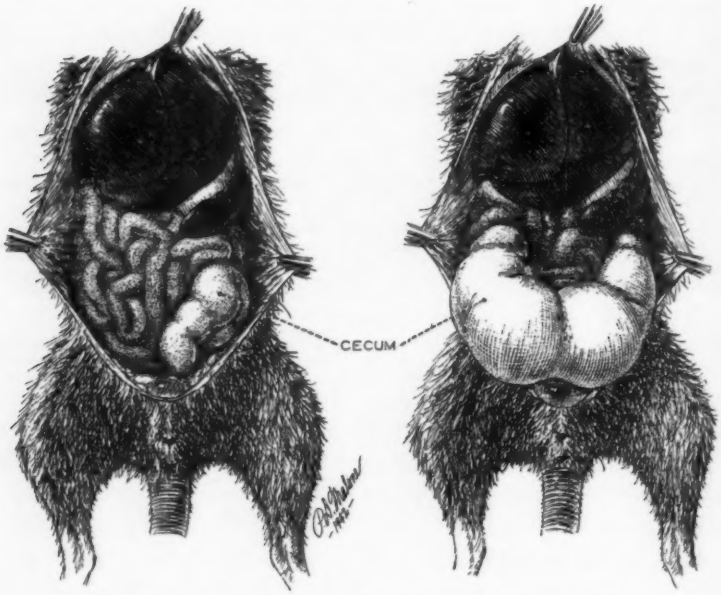

FIG. 9. DRAWING SHOWING THE CECUM OF A NORMAL RAT AND OF A PANCREATECTOMIZED RAT

(31 as compared to 23 per cent) and about half as much fat (39 as compared to 68 per cent) as did the yeast-fed rats.

After pancreatectomy the yeast-fed rats showed no increase in water intake while the rats offered the vitamin B components showed approximately a 70 per cent increase. Placed on the stock diet the rats in the vitamin B-fed group drank approximately $2\frac{1}{2}$ times as much water as during the preoperative period.

Anatomical Changes

Lens Cataracts. After we had completed our observations on the effects of the various experimental diets and the rats had been maintained for some months on the stock diet, they were killed and autopsied.

All of the rats showed lenticular cataracts. Those cataracts which were in the early stages were characterized by the presence of large clusters of subcapsular vacuoles in the anterior cortex and lens periphery, similar to the early stages of galactose cataracts, while those in the later stages showed typical mature formations.[4]

Enlarged Cecum. Of special interest was the finding at autopsy that most of the rats had a much enlarged cecum which was filled with a solid mass of finely granular, fatty, partly digested food. Figure 9 shows a drawing of a normal cecum and of a cecum of one of these rats which had been pancreatectomized 250 days before. In some of the rats the cecum occupied almost the entire abdominal cavity.

DISCUSSION

On the basis of the results of our present and previous self-selection experiments, and of biochemical studies, we shall now attempt to formulate the various factors involved in the production of diabetes following sub-total pancreatectomy in the rat. This will be done first for rats kept on the stock diet in which they are forced to take the ingredients of their diet in fixed proportions, and then for rats which are given full opportunity to regulate the amount of each ingredient that they ingest. For the discussion of the mechanisms involved in the two dietary situations it is important to keep in mind a fundamental concept of self regulatory dietary selection, that rats eat in the first place to get calories (7). The results of the present experiments show, however, that rats do not eat simply for calories, but for utilizable calories.

[4] Dr. Wilhelm H. Buschke of the Wilmer Clinic, Johns Hopkins Hospital, kindly examined these eyes for us. He has described some of these lesions in two papers on cataracts (Classification of Experimental Cataracts in the Rat, Arch. Ophth., **30:** 735, 1943. Dystrophic Cataracts and their Relation to other 'Metabolic' Cataracts, Arch. Ophth., **30:** 751, 1943).

Thus on the stock diet, the pancreatectomized rats, which on account of the lack of insulin are no longer able to utilize carbohydrate in their diet, eat larger amounts of the diet to obtain calories from the fat which they can utilize. This is the cause of diabetic polyphagia. The ingested carbohydrate cannot be used by the muscles and so remains in the blood stream in large amounts. Through the mechanism which strives to maintain the constancy of the internal environment, the kidneys excrete a large part of the excess sugar. The large amount of water required in this operation leaves the body along with the sugar, thus causing the polyuria of diabetes. The subsequent state of general dehydration involving all of the tissues of the body includes the membranes of the mouth and throat. The resulting sensation of thirst stimulates the animal to drink large amounts of water. This brings about the polydipsia of diabetes. Like the polydipsia of diabetes insipidus it is secondary to the polyuria (8, 9). After pancreatectomy protein is lost, as is shown by the increased nitrogen output in the urine. The increased amount of protein obtained when the animals have satisfied their caloric needs is not sufficient to replace all of the lost body protein. The animals therefore lose weight. Finally, being forced to take large amounts of carbohydrate which they can not utilize and smaller amounts of fat and protein, and also being forced to use part of their energy in ridding the body of the unabsorbed carbohydrate, the rats become almost totally inactive.

When allowed to select the ingredients of their diet the rats take only small amounts of the carbohydrate which they cannot utilize without insulin. They take increased amounts of fat and protein which they can utilize and so do not develop the diabetic polyphagia. The components of the vitamin B complex which they take in increased amounts apparently help them to utilize the carbohydrate and particularly the large amounts of protein. On account of the low carbohydrate intake blood sugar is not increased, water is not needed in the excretion of excess sugar, and hence polyuria and polydipsia develop only in a slight degree or not at all. The high amounts of ingested fat are transformed into energy, as is demonstrated by high levels of running activity.

From the fields of biochemistry and medicine numerous observations show that diabetic animals and patients are able to utilize fat. In

the pre-insulin period many clinicians found that diabetic patients improved on high fat and low carbohydrate diets. Thus, Allen stated in 1917: "Notwithstanding that fat ingestion has been proved to create or increase ketonuria in both normal persons and diabetics, fat has remained the one unrestricted food in diabetes. Even Forssner saw reasons to justify the prevailing treatment, considering that tolerance for fat is acquired, that its addition to protein then increases ketonuria by only a few grams, and that its use is preferable to undernutrition. Naunyn, von Noorden and others have agreed that fat should be withdrawn only in the presence of threatened coma. The few writers who have advocated occasional restriction of fat have merely favored limiting it to the caloric requirement of a maintenance diet. The more common practice has been to push fat by all possible devices to the utmost limit of the digestive power, with the idea of building up strength and nutrition. Another support for the fat diet was given in the statement that the heaviest fat feeding only slightly increases the combustion of fat, the surplus being stored" (10). Newburgh and Marsh (11) and Petrén (12) were the first to advocate the use of these diets which were later widely used by other clinicians. Newburgh and Marsh found in 1920 that none of the 73 patients whom they treated with a high fat diet developed a severe acidosis. Evidence of acidosis decreased progressively day by day until it had invariably become negligible. Joslin (13) stated, "Fat has formed the bulk of the diabetic patient's diet. In the normal diet it furnishes less than one-third of the total calories and today in the diabetic diet it forms about one-half.

"It is surprising how readily in the past double and even treble the quantity of fat ingested by normal individuals was borne by the stomach of the diabetic patient. . . .

"Oil is an ideal diabetic food, because it is a pure fat and Italian patients naturally bear olive oil unusually well. An Italian diabetic patient under my care at the Boston City Hospital with typhoid fever not only passed through the disease uneventfully more than twenty years ago upon oatmeal gruel and olive oil, but incidentally became sugar free and developed no acidosis."

Best, Haist, and Radout (14); Haist and Best (15); Haist and Campbell and Best (16) showed that the insulin content of the islets was

smaller when rats were kept on a high fat diet. They concluded that the fat "rested" the islet cells. It follows that on a high fat diet the rats have a reduced need for insulin.

Marks and Young (17) found dogs rendered diabetic by daily injection of anterior pituitary extract lost most of their glycosuria and ketonuria when kept on a diet consisting almost exclusively of fat. These observations were confirmed by Dohan and Lukens (18).

Recently Burn, Lewis and Kelsey reported (19) that alloxan diabetes in the rat could be kept under complete control by the administration of a high fat diet (80–90 per cent margarine, 10–20 per cent casein).

Clinicians have shown less agreement in regard to the protein needs of diabetic patients. In general they have advocated sufficient amounts of protein to keep the body in nitrogen balance. Bouchardat (20) reduced the carbohydrate intake of his patients to a minimum and recommended a gluten bread to supply the protein. Cantani (21) strongly advocated the elimination of carbohydrates and the almost exclusive use of meat and fat. Naunym (22) and later Newburgh and Marsh (11) and others have advocated low protein diets. It must be kept in mind here that many of the beliefs regarding dietary treatment of diabetics had their origin not only in the pre-insulin but in the pre-vitamin period. It is possible that the high amounts of thiamine may help the diabetic to utilize at least some of the carbohydrate but more particularly that it may help to utilize the higher amounts of protein. Results obtained with other self-selection studies have shown that thiamine plays an important part in the utilization of protein as well as of carbohydrate (23). On the so-called single food choice diet rats indicated by their appetites that they needed approximately 13 times as much thiamine for the utilization of the protein casein as for the carbohydrate dextrose. The other components of the vitamin B complex also play a definite part in the utilization of protein (3).

Some clinicians have reported that thiamine has a definitely beneficial effect on diabetics (24, 25, 26), while others have reported that it has little or no effect whatever (27, 28, 29, 30, 31). To our knowledge it has not been tried with high protein diets.

It is possible that the rats might have thrived even better on their selections had the assortment of substances offered for choice included several other essential elements of the diet. In the first place we may

consider here the fact that casein, the only protein available, did not contain adequate amounts of the essential amino acids tryptophane and cystine; and according to von Noorden (32) it is much more apt to produce glycosuria than other proteins such as egg albumen and albumen from cereals (wheat, rye, rice, and oats). It must also be considered that olive oil may not contain adequate amounts of some of the essential fatty acids. Had the rats had access to butter in place of olive oil or other fats (33) they might have shown fewer diabetic symptoms. The contrary is also possible, however: that the good results obtained may have depended on the use of olive oil in keeping with Joslin's experience with his Italian patients. Other fats might not have given such favorable results. The self-selection diet lacked such minerals as copper, iron and cobalt, all of which have been reported to play a part in the metabolism of diabetes; also it did not contain lipocaiac which is known to be present in yeast.

The temporal relationship between the changes in appetite for the various substances is worthy of special comment. The rats started to eat more protein and more of the various components of the vitamin B complex almost at once after pancreatectomy, but they did not refuse the carbohydrate and manifest an abnormal appetite for fat until several weeks postoperatively. From these experiments it is not clear whether the rats changed their appetites because of altered taste for the food or because they felt better after the ingestion of certain foods, not of others. It must also be considered that the appetites for fat and carbohydrate did not change at once on account of the food habits of the rat, the tendency being to continue to eat from a familiar container for some time after the contents have been changed.

The results of our experiments indicate that the ability as well as the urge of pancreatectomized rats to take exercise depends largely on the presence of a high amount of fat in the diet.[5]

[5] Dr. Walter Fleischmann of the Harriet Lane Home for Children has kindly given us the following note which has a special interest in this connection. "The distinguished Viennese physiologist, Professor Arnold Durig, was a mild diabetic, consistently spilling sugar and occasionally showing acetonuria. He never used insulin. As a man in his fifties he used to do a lot of mountaineering during his vacations often climbing or skiing in altitudes from 6,000 to 9,000 feet as long as

It is noteworthy that although diabetics have been found to thrive on high fat diets no instances have been reported in which they manifested a marked craving for fat or substances with a high fat content. On the contrary it has often been observed that they manifest a great appetite for sugar and candies. It is possible that human beings are not capable of making such beneficial dietary selections as are made by rats, on account of defective taste mechanisms (1). It is also likely, however, that cultural ideas in regard to the eating of pure fat may deter them from eating large amounts of lard or suet, or drinking great quantities of olive oil. It is also possible that being in great need of calories they take pure carbohydrate such as candy with a high energy content even though they are able to utilize only a part of them. It must be recalled here that on the self-selection diet most of the rats manifested an increased carbohydrate appetite for a short interval immediately after pancreatectomy. Human diabetics who have access only to a diet of natural, unpurified foods, which allows only a limited degree of selection, may remain indefinitely in this stage in which the carbohydrate appetite predominates.

Thus, in summary, the diabetic rats have indicated by their appetites that they do not need carbohydrate but do need large amounts of fat. These appetites are thus in full agreement with the clinical observations made during the pre-insulin period. By their appetites the rats have indicated also that they need large amounts of protein and of several components of the vitamin B complex. This need for large amounts of protein does not coincide with clinical observations, but it must be remembered that clinically high amounts of protein were not used with high amounts of the various components of the vitamin B complex. In this instance the reliability of the rat's appetite as a guide to dietary needs will have to await the results of clinical observations in which a moderately high fat diet is combined with a high protein and high vitamin B diet.

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10 hours a day. He told me and other members of his staff that during these tours his only food consisted of lard with only an occasional dried prune to quench his thirst. He claimed that this diet was essential for his ability to climb the highest peak in the Austrian Alps".

Recent discussions of the part played by exercise in the control of diabetes have dealt only with insulin and its relation to carbohydrate metabolism (34, 35).

SUMMARY

1. Eight adult female rats were given access to an assortment of 14 substances in separate containers—casein, dextrose, olive oil, 5 different mineral solutions, 6 different solutions of vitamin B components, cod-liver oil, and tap water. They ingested large amounts of carbohydrate, moderate amounts of protein, and minimal amounts of fat. On these dietary selections they gained weight and remained in good health.

2. After sub-total pancreatectomy they immediately started to take more protein and more of the various components of the vitamin B complex. Several weeks later they took large amounts of fat and greatly reduced their carbohydrate intake. They continued to ingest large amounts of thiamine hydrochloride, pantothenic acid and pyridoxine, but did not increase their appetite for any of the minerals with the possible exception of calcium and magnesium.

3. So long as they remained on the self-selection diet they did not show any definite symptoms of diabetes. When placed on the stock diet, however, and thus forced to take the various ingredients in fixed amounts, marked symptoms of diabetes appeared almost at once, chiefly polyphagia and polydipsia.

4. Rats which had become very inactive after pancreatectomy began to be active again on a diet which was high in protein and in the various components of the vitamin B complex and in olive oil, but only after olive oil was added. Fat seemed to play the essential part in the production of spontaneous activity.

5. After being placed on the stock diet the rats developed marked lenticular cataracts of the galactose type and at autopsy they were found to have greatly enlarged ceca filled with granular, partially digested food.

REFERENCES

1. RICHTER, C. P.: Total Self Regulatory Functions in Animals and Human Beings. The Harvey Lectures Series, **XXXVIII:** 63, 1942–1943.
2. RICHTER, C. P., AND E. C. H. SCHMIDT, JR.: Increased Fat and Decreased Carbohydrate Appetite of Pancreatectomized Rats. Endocrinology, **28:** 179, 1941.
3. RICHTER, C. P., AND C. D. HAWKES: The Dependence of the Carbohydrate, Fat, and Protein Appetite of Rats on the Various Components of the Vitamin B Complex. Am. J. Physiol., **131:** 639, 1941.

4. SHAPIRO, R., AND G. PINCUS: Pancreatic Diabetes and Hypophysectomy in the Rat. Proc. Soc. Exp. Biol. and Med., **34:** 416, 1936.
5. RICHTER, C. P., AND E. C. H. SCHMIDT, JR.: Behavior and Anatomical Changes Produced in Rats by Pancreatectomy. Endocrinology, **25:** 698, 1939.
6. RICHTER, C. P.: The Nutritional Value of Some Common Carbohydrates, Fats and Proteins Studied in Rats by the Single Food Choice Method. Am. J. Physiol., **133:** 29, 1941.
7. RICHTER, C. P.: Alcohol as a Food. Quart. J. Studies on Alcohol, **1:** 650, 1941.
8. RICHTER, C. P.: The Primacy of Polyuria in Diabetes Insipidus. Am. J. Physiol., **112:** 481, 1935.
9. RICHTER, C. P., AND J. F. ECKERT: Further Evidence for the Primacy of Polyuria in Diabetes Insipidus. Am. J. Physiol., **113:** 578, 1935.
10. ALLEN, F. M.: The Rôle of Fat in Diabetes. Am. J. Med. Sci., **153:** 313, 1917.
11. a) NEWBURGH, L. H., AND P. L. MARSH: The Use of a High Fat Diet in the Treatment of Diabetes Mellitus. First Paper. Arch. Inter. Med., **26:** 647, 1920.
    b) NEWBURGH, L. H., AND P. L. MARSH: The Use of a High Fat Diet in the Treatment of Diabetes Mellitus. Second Paper. Blood Sugar. Arch. Inter. Med., **27:** 699, 1921.
12. PETRÉN, K., AND OTHERS: Studies on Diabetes. J. Metabol. Res., **5:** 7, 1925.
13. JOSLIN, E. P.: The Treatment of Diabetes Mellitus. Philadelphia, Lea and Febiger, 1937, p. 232.
14. BEST, C. H., R. E. HAIST AND J. H. RIDOUT: Diet and Insulin Content of the Pancreas. J. Physiol., **97:** 107, 1939.
15. HAIST, R. E., AND C. H. BEST: Factors Affecting Insulin Content of the Pancreas. Science, **91:** 410, 1940.
16. HAIST, R. E., J. CAMPBELL AND C. H. BEST: Prevention of Diabetes. New Engl. J. Med., **223:** 607, 1940.
17. MARKS, H. P., AND F. G. YOUNG: Observations on the Metabolism of Dogs Made Permanently Diabetic by Treatment with Anterior Pituitary Extract. J. Endocrinology, **1:** 470, 1939.
18. DOHAN, F. C., AND F. D. W. LUKENS: Persistent Diabetes Following the Injection of Anterior Pituitary Extract. Am. J. Physiol., **125:** 188, 1939.
19. BURN, J. H., T. H. C. LEWIS AND F. D. KELSEY: The Dietary Control of Alloxan Diabetes in Rats. Brit. Med. J., No. 4379, 752, 1944.
20. BOUCHARDAT, A.: Traité d'Hygiène Publique et Privée. Paris, Librairie Germer Baillière et cie., 1881.
21. CANTANI, A.: Der Diabetes Mellitus. Berlin, Denicke's Verlag. (G. Reinke), 1877.
22. NAUNYN, B.: Der Diabetes Melitis. Ed. 2, Wien, A. Holder, 1906.
23. RICHTER, C. P., AND K. K. RICE: Comparison of the Nutritive Value of Dextrose and Casein and of the Effects Produced on their Utilization by Thiamine. Am. J. Physiol., **141:** 346, 1944.

24. VORHAUS, M. G., R. R. WILLIAMS AND R. E. WATERMAN: Studies on Crystalline Vitamin B_1: Observations in Diabetes. Am. J. Dig. Dis. and Nut., **2:** 541, 1935.
25. DIENST, C.: Ist der Diabetes durch die Vitamine B und C beeinflussbar? Deutsche Med. Wchnschr., **65:** 710, 1939.
26. PFLEGER, R., AND F. SCHOLL: Diabetes und Vitamin C. Wien. Archiv. f. inn. Med., **31:** 219, 1937.
27. VORHAUS, M. G.: Present Evaluation of Vitamin B_1 Therapy. Am. J. Dig. Dis. and Nut., **3:** 915, 1937.
28. OWENS, L. B., S. S. ROCKWERN AND E. G. BROWN: Evaluation of Vitamin B Therapy for Diabetes. Arch. Int. Med., **66:** 679, 1940.
29. TRASOFF, A., AND C. BORDIN: The Use of Vitamin B_1 in Diabetes Mellitus: A Clinical Study. Am. J. Dig. Dis., **8:** 1, 1941.
30. JACKSON, R. L., AND I. BARTH: Effect of Adding the Vitamin B Complex to the Diets of Stabilized Diabetic Children. Am. J. Dis. Child., **62:** 516, 1941.
31. ROBSON, G. B., W. C. CUTTING AND H. GRAY: The Effect of the Vitamin B Complex in Diabetes Mellitus. J. Clin. Endo., **2:** 262, 1942.
32. VON NOORDEN, C.: Clinical Treatises on the Pathology and Therapy of Disorders of Metabolism and Nutrition. New York, E. B. Treat and Company, 1907.
33. STADIE, W. C.: Fat Metabolism in Diabetes Mellitus. Ann. of Int. Med., **15:** 783, 1941.
34. RICHARDSON, R.: Factors Determining the Effect of Exercise on Blood Sugar in the Diabetic. J. Clin. Inv., **13:** 949, 1934.
35. MARBLE, A., AND R. M. SMITH: Exercise in Diabetes Mellitus. Arch. Int. Med., **58:** 577, 1936.

BOOKS RECEIVED FOR REVIEW

Clinical Lectures on the Gallbladder and Bile Ducts. By SAMUEL WEISS. 504 pp. Price $5.50. The Year Book Publishers, Inc. 304 South Dearborn Street, Chicago.

Doctors at War. By MORRIS FISHBEIN. 418 pp. Price $5.00. E. P. Dutton & Company, Inc. New York, 1945.

Experimental Basis for Neurotic Behavior. By W. H. GANTT. 198 pages. Price $4.50. Paul B. Hoeber, Inc., New York and London, 1944. (When this book was reviewed in December, 1944 the publisher's name was omitted.)

Operations of General Surgery. By THOMAS G. ORR. 723 pp. Price $10.00. W. B. Saunders Company, Philadelphia, 1944.

Patients Have Families. By HENRY B. RICHARDSON. 407 pp. Price $3.00. The Commonwealth Fund, New York, 1945.

Peripheral Nerve Injuries. By WEBB HAYMAKER and BARNES WOODHALL. 227 pp. Price $4.50. W. B. Saunders Company, Philadelphia.

Proceedings of the Rudolf Virchow Medical Society in the City of New York. Volume III. By FRANZ M. GROEDEL, BRUNO KISCH, and ERWIN SCHIFF. 103 pp. Price $2.00. Brooklyn Medical Press, 2700 Broadway, New York, 1945.

The Story of a Hospital: The Neurological Institute of New York, 1909–1938. By CHARLES A. ELSBERG, 174 pp. Price $3.50. New York, Paul B. Hoeber, Inc., 1944.

Surgical Disorders of the Chest: Diagnosis and Treatment. By J. K. DONALDSON. 364 pp. Price $6.50. Philadelphia, Lea and Febiger, 1944.

Textbook of Abnormal Psychology. By ROY M. DORCUS and G. WILSON SHAFFER. Third Ed. 547 pp. Price $4.00. The Williams & Wilkins Company, Baltimore, 1945.

The Woman Asks the Doctor. By EMIL NOVAK. 130 pp. Price $1.50. The William & Wilkins Co., Baltimore, 1944. 2nd Ed.